

GB993125

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Desc

Claims

BEST AVAILABLE COPY**Novel pharmaceutical compositions for the treatment of fatigue**

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Inventor(s):

Applicant(s): CFMC

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Equivalents:

Abstract

Pharmaceutical compositions for the treatment of fatigue comprise phosphocreatine or phosphocreatinine e.g. as their disodium salts or their acid addition salts with an amino alcohol, and a solid diluent or carrier. Non-toxic salts of succinic acid and potassium may also be present. They may be in orally administrable forms, e.g. cachets.

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PATENT SPECIFICATION

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NO DRAWINGS.

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SPECIFICATION NO. 993,125

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of ETABLISSEMENTS KUHLMANN, a French body corporate, of 25 Boulevard de l'Amiral Bruix, Paris 16^eme, France.

THE PATENT OFFICE

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- 5 declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- 10 The present invention concerns novel pharmaceutical compositions for the treatment of fatigue. The importance of phosphocreatine or phosphagen in the course of muscular contraction, and particularly of cardiac action, is well known. In man this phosphagen constitutes a form of reserve energy, owing to the linkage rich in energy which its molecule contains. This energy is rapidly and easily utilisable for numerous metabolic reactions, such as muscular contraction, or for numerous synthesis reactions through the rephosphorylating of the adenosine diphosphate with phosphorylated groups. However, phosphocreatine has not been proposed until now as a substance for the treatment of fatigue. Now, it has been found that, with administration either as salts of phosphocreatine or as salts of phosphocreatinine, it is possible to combat fatigue with great efficacy; by varying the posology, the source of energy which it requires to reconstitute its metabolic reserves can be placed at the disposal of the organism.
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According to the present invention therefore pharmaceutical compositions for the treatment of fatigue are provided containing a salt of phosphocreatine and/or a salt of phosphocreatinine with a pharmaceutically acceptable solid carrier.

However, fatigue is a syndrome which is characterised by disturbances affecting the [Pric

creatine or of phosphocreatinine with products acting at the nervous level and/or with products acting at the general metabolism level.

As a product acting against nervous fatigue the succinate of dimethylcolamine, methylcolamine or colamine may be used. Potassium succinate can be used as a product acting at the level of general metabolism.

At the level of general metabolism, the succinic ion (in the form, for example, of potassium succinate or the succinate of methylcolamine) plays an important part in reducing fatigue. Its important metabolic turnover makes it an excellent source of metabolites; it is in fact a very important component of the Krebs cycle. This series of reactions represents the essential source of energy used by the organism for all the endergonic processes such as biochemical syntheses and muscular contraction. It may therefore be thought—and our pharmacodynamic experiments have demonstrated this to perfection—that the administration of succinate, and more particularly potassium succinate, by encouraging this creation of energy, has an interesting anti-fatigue action.

The potassium cation for its part is essential to cell life and plays an important part in muscular contraction. The state of fatigue is bound up with disturbances in the potassium-sodium ionic equilibrium, the decontraction being related particularly to the recharging of the muscular fibre with potassium. The potassium cation can be introduced into the anti-fatigue compositions of the present invention not only in the form

of potassium succinate but in the form of potassium fumarate.

Methylcolamine (in the form of methylcolamine succinate, for example), the precursor of choline and an integral part of the choline cycle, reduces nervous fatigue.

The preferred salts of phosphocreatine and phosphocreatinine, namely sodium phosphocreatinate and sodium phosphocreatininate, have practically no toxicity, either taken orally or by injection. Neutral potassium succinate has a slight toxicity (on adult mice, maximum non-toxic dose of 1 gram per kilogram of animal, 50% lethal dose of 2.30 grams per kilogram. The acid succinate of N-methyl-colamine has practically no toxicity.

The invention will be more clearly understood by reference to the following examples which are purely illustrative.

EXAMPLE 1.

A powder containing 25.42 grams of sodium phosphocreatinate with four molecules of water of crystallization, 70.62 grams of neutral potassium succinate and 4.96 grams of acid succinate of N-methyl-colamine is prepared in a mixer. The mixing is continued with exclusion of moisture until a homogeneous powder is obtained. This powder is divided into cachets, which can be packaged in the dry state, at the rate of 354 milligrams per cachet. The cachets are then conditioned and kept free from moisture.

These cachets have been administered to subjects suffering from various types of fatigue, in particular to subjects suffering from post-infectious asthenia and excellent results have been achieved.

EXAMPLE 2.

A mixture of sodium phosphocreatinate, neutral potassium succinate and acid succinate of N-methylcolamine has been tested on emaciated, fatigued or convalescent people who are unfit for regular work. The posology has been at the beginning of 40 centigrams of sodium phosphocreatinate, 100 centigrams of potassium succinate and 28 milligrams of succinate of N-methylcolamine, per day for 4 days, then a second treatment after a rest of 4 days if a significant result was not obtained at first. The results were mostly sufficiently satisfactory to avoid the necessity of a continuation of the treatment.

In view of the low toxicity of the product, 56 milligrams per day of succinate of N-methylcolamine were administered in the majority of cases instead of 28.

The tolerance to the different doses used was excellent (25 out of 26). There has not been any troublesome therapeutic incidence on the blood count, but on the contrary, in certain cases a slight increase of the erythrocytes and a tendency to restore the leucocytes figure to normal have been observed.

The clinical results were excellent in the same proportions (25 out of 26). The patients stated that they very quickly felt a sensation of well-being, of relief, and disappearance of their fatigue.

With 12 patients the experimenters have been able to verify a very distinct return of weight. In other respects, the medical treatment in certain cases had a favourable action on hepatic flocculation tests, while the arterial pressure was practically unmodified.

The experimenters have thus been able to declare categorically in favour of the good tolerance and the marked anti-fatigue therapeutic properties of the above composition.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition for the treatment of fatigue containing a salt of phosphocreatine and/or a salt of phosphocreatinine together with a pharmaceutically acceptable solid carrier.

2. A pharmaceutical composition as claimed in claim 1 containing potassium fumarate, potassium succinate, colamine succinate, methyl-colamine succinate or dimethylcolamine succinate.

3. Pharmaceutical compositions as claimed in claim 1 or 2 in which the salt of phosphocreatine is the sodium salt.

4. Pharmaceutical compositions as claimed in claim 1, 2 or 3 in which the salt of phosphocreatinine is the sodium salt.

5. Pharmaceutical compositions having a therapeutic action against fatigue substantially as herein described with reference to and as illustrated in either of the Examples.

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